IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Hamdi K. Hamdi et al.	Confirmation No.	9959
Serial No.:	10/712,423	Art Unit:	1614
Filed:	November 13, 2003	Examiner:	Shirley V. Gembeh
For:	Methods for Inhibiting Cancer & Scar Formation		

DECLARATION OF HAMDI K. HAMDI UNDER 37 C.F.R. 1.132

I, Hamdi K. Hamdi, declare that:

1. I am a co-inventor of the present continuation-in-part patent application, and the related parent application, namely, United States Patent Application Serial Number 10/153,003, filed May 22, 2002 and now issued as United States Patent Number 6,632,798, issued on October 14, 2003. A copy of my curriculum vitae is attached hereto as Exhibit A. I have reviewed the Office Action dated June 20, 2006, issued in relation to the present application.
2. Based upon my review of the Office Action, it appears as though the Examiner has taken the position that based on current anti-cancer drug screening processes the pharmaceutical art is unpredictable. In particular, the Examiner points to the unpredictability between *in vitro* and *in vivo* success and the faultiness of the *in vitro* and *in vivo* assays commonly used to discover and predict the efficacy of cancer drugs.
3. Certain methods within the pharmaceutical art are unpredictable because the intellectual approach used in the design of these methods was unsound. In particular, the Gura and Johnson et al. references provided by the Examiner utilized methods relying on the use of xenografts, the targeting of specific gene products, compounds that kill cancer cells but have a high toxicity, and/or the inhibition of cell growth.

4. Using xenografts leads to faulty results since the interaction of cancer and immunity is crucial to the spread and/or suppression of cancer. Gene targeted therapies are illogical due to the redundancy of biological systems. The use of toxic compounds presents problems with obtaining a sufficient level of the compound within the patient in order to kill the cancer cells. There are many growth pathways which cancer cells can use, and thus, the use of anti-growth compounds is illogical due to the redundancy.

5. Current cancer drug screening methods fail to provide efficacious cancer drugs. A major reason why *in vitro* assays are non predictive of *in vivo*/clinical outcomes is due to the failure in achieving the active concentration needed to obtain efficacy in the body, which is much higher than what was used *in vitro*. This higher dose is needed to compensate for organismal physiology, which limits bioavailability. Such limitations do not exist *in vitro*. Because most compounds are toxic, these higher concentrations cannot be reached physiologically without causing harm to the organism.

6. The compounds disclosed and claimed in the present invention are non-toxic and therefore the bioavailability limit does not apply and high doses can be administered. Thus, non-toxic compounds are able to approximate their *in vitro* behavior by bypassing the limitations of their pharmokinetics.

7. Although cancer is a complex disease with multiple gene triggers, there are unifying principles that may be utilized in order to treat all types of cancer. The claims of the present continuation-in-part application are directed to methods of affecting the cytoskeleton of animal cells and treating cancer.

8. The compounds disclosed and claimed in the present invention target a non-redundant biological structure, i.e., the cytoskeleton, which is essential for cell survival. Cellular morphology and invasiveness are dependent on the cytoskeleton, which is common to all cells. It is an integral part of the cell contributing to all its physiological activity. The cytoskeleton plays a major role in cellular division, movement, and feeding, thus disrupting the cytoskeleton has a global effect on all cell activity. Thus, the claimed

compositions has an effect on all cancer cell types, unlike anti-cancer compositions known in the prior art.

9. Further studies have confirmed the accuracy of our *in vitro* method for use *in vivo*. The currently claimed compounds have successfully regressed tumors *in vivo* in both animals and humans without any recurrences. In particular, the mouse model used developed tumors spontaneously and without human intervention, unlike the xenograft models of the prior art.

10. The mice were administered a 1% solution of a claimed compound in their drinking water for a period of nine to twelve days. After the treatment period, the tumors were completely regressed and the mice survived to a normal life span and reproduced normally.

11. Favorable treatment using a claimed compound has been shown in human tumors including primary and secondary liver, sarcoma, glioma, astrocytoma, leukemia, lymphoma, pancreatic, colon, lung, mesothelioma, ovarian, breast, prostate, GIST, neurofibromatosis and papilloma.

12. One example includes an 84 year old male with multiple pancreatic tumors and abdominal metastases. A claimed compound, oleuropein, was orally administered for seven weeks and no side effects were reported. At week seven, MRI scans showed all tumors had disappeared. No recurrence has been determined sixteen months later.

13. Another example includes a 53 year old male with prostatic adenocarcinoma extracapsular disease. A subsequent bone scan showed a metastasis on the right symphysis pubis. A claimed compound, oleuropein, was administered orally for over eight months without reported side effects. By week six, the patients PSA had dropped significantly. By the eighth month, a new bone scan showed disappearance of the pubic metastasis and the PSA score remained low over a year later.

14. Another example includes a 16 year old male with a 10x14 cm osteosarcoma on the dorsal area of the knee with tibial involvement. The claimed compound, oleuropein, was administered orally for eight weeks and no side effects were reported. Within two weeks, the tumor started to

lose its hard consistency and the area showed reduced inflammation and pain. Within four weeks, the tumor was significantly softer. At six weeks, the tumor detached from the tibia and surrounding structures, and was left hanging within the attached skin. By eight weeks, the tumor was assessed as greater than 90% dead by multiple MRI scans and biopsy. The tumor was then surgically removed and determined to lack tumor viability.

15. Yet another example includes a 56 year old female with breast carcinoma. The claimed compound was administered orally for over twelve weeks with no side effects reported. At week twelve, the tumor was resected and found to consist entirely of dead cells.

16. Based upon the above disclosed properties, the aforementioned clinical results, and my knowledge of the compounds, it is believed that compounds as claimed in the patent are effective and are suitable for the treatment of cancers.

17. I hereby declare that all statements made herein are of my own knowledge, are true, and that all statements made under information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Respectfully submitted,

Date: October 20, 2006 By: Hamdi K. Hamdi

Hamdi K. Hamdi

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Curriculum Vitae

Hamdi Khalil Hamdi, Ph.D.

Office Address: SAFICOR, 1920 E. Katella ave, Suite U, Orange CA 92867; **Email:** hkhamdi@saficor.com or hhamdi@gmail.com

RESIDENCE: U.S. Citizen

PROFESSIONAL EXPERIENCE:

2004-present	President & CEO, SAFICOR
2002-2004	Research Assistant Professor, UCI Medical Center
2000-2002	Post-doctoral fellow, Cedars-Sinai Medical Center, Los Angeles
1999-2000	Post-doctoral Researcher, Department of Pediatrics, UCLA Medical School, Los Angeles, CA.
1994- 1999	Research Assistant-Doctoral Research, University of California Riverside
1992- 1994	Research Associate, Cedars-Sinai Medical Center
1990- 1992	Research Assistant, VA Medical Center, Long Beach
1989- 1990	Research Assistant, California State University Long Beach

TEACHING EXPERIENCE

2002-present	Training undergraduate and medical students, residents and fellows.
1994-1999	Teaching Assistant-Dept. of Biochemistry, UC Riverside
1998	Part-time Assistant Professor, California State University Long Beach

MAJOR RESEARCH INTERESTS:

1- Drug Discovery for vascular diseases and Cancer.

2- Age-Related diseases including Macular Degeneration (AMD) and Alzheimer's disease (AD). The role of genetic polymorphism in the human population and its predisposition/ or protection in diseases of age.

3- Testing algorithms for identifying genes in the human genome. Incorporating these algorithms into user friendly software.

4- Discovering and classifying human DNA repeats into polymorphic/phylogenetic distributions from the wealth of sequence information available on the human genome. Currently wrote and developed software for classifying these sequences.

DEGREES:

1995-1999	Doctor of Philosophy, Biochemistry, 1999 University of California- Riverside, Riverside, California
1982-1986	Bachelor of Science, University of Illinois--Chicago, Chicago, Illinois.

SOFTWARE DEVELOPMENT:

1-DNA alignment program **2**-Phylogeny of DNA repeats **3**-DNA reverse compliment **4**-Encryption software **5**-Software for screening anti-cancer compounds using structural analysis..**6**-DNA analysis macros and software.

PEER-REVIEWED PUBLICATIONS:

1. Castellon R. and **Hamdi HK,** Demystifying the ACE polymorphism: from genetics to biology. Current Pharamceutical Research. *Publication in press.*

2. Hamdi HK and Castellon R, Oleuropein, a non-toxic olive iridoid, is an anti-tumor agent and cytoskeleton disruptor. Biochem Biophys Res Commun. 2005 Sep 2;334(3):769-78.

3. Hamdi HK, Castellon R. A genetic variant of ACE increases cell survival: a new paradigm for biology and disease. Biochem Biophys Res Commun. **2004** May 21;318(1):187-91.

4. Hamdi HK, and Castellon R. ACE inhibition actively promotes cell survival by altering gene expression. Biochem Biophys Res Commun. **2003** Oct 31; 310(4): 1227-35.
5. Hamdi HK and Kenney MC. Age-related macular degeneration: A new viewpoint *Frontiers in Bioscience* **2003** May 1; 8:e305-14.
6. Hamdi HK, Reznik J, Castellon R, Atilano SR, Ong JM, Udar N, Tavis JH, Aoki AM, Nesburn AB, Boyer DS, Small KW, Brown DJ, Kenney MC. Alu DNA polymorphism in ACE gene is protective for age-related macular degeneration. Biochem Biophys Res Commun. **2002** Jul 19; 295(3): 668-72.
7. Castellon R, **Hamdi HK**, Sacerio I, Aoki AM, Kenney MC, Ljubimov AV. Effects of angiogenic growth factor combinations on retinal endothelial cells. Exp Eye Res. **2002** Apr; 74(4): 523-35.
8. Castellon R, Caballero S, **Hamdi HK**, Atilano SR, Aoki AM, Tarnuzzer RW, Kenney MC, Grant MB, Ljubimov AV. Effects of tenascin-C on normal and diabetic retinal endothelial cells in culture. Invest Ophthalmol Vis Sci. **2002** Aug; 43(8): 2758-66.
9. Hamdi HK , Tavis J. and Dugaiczyk A. Alu-mediated phylogenetic novelties in gene regulation and development. *J Mol Biol.* **2000**; 299(4): 931-939.
10. Nishio, H., **Hamdi HK.**, and Dugaiczyk A. Genomic expansion across the albumin gene family on human chromosome 4q is directional. *Biol. Chem* **1999**; 380(12): 1431-1434.
11. Hamdi HK, Nishio H, Zielinski R, and Dugaiczyk A. Evolutionary origin and phylogenetic distribution of Alu DNA sequences: Irreversible events in the evolution of primates, *J Mol Biol.* **1999**;289(4):861-871.
12. Brown DJ, Bishop P., **Hamdi H.**, and Kenney MC. Cleavage of structural components of mammalian vitreous by endogenous matrix metalloproteinase-2. *Current Eye Research* **1996**; 15(4):439-445.
13. Hamdi HK, Bergis F, Brown DJ, and Kenney MC. Proteinase activity in normal human tears- male-female dimorphism. *Current Eye Research* **1995**; 14(12): 1081-1086.
14. Brown D, **Hamdi H**, Bahri S, and Kenney MC. Characterization of an endogenous metalloproteinase in human vitreous. *Current Eye Research* **1994**; 13(9): 639-647.

CONFERENCES (Published Abstracts):

1-H.J. Kostamaa, Z.Baharoglu, J.H. Tavis, S.E. Anorve, A.S. Ratnayake, D.S. H. Kim, G.Resende, S.Blacka, D.S. Boyer, H.K. Hamdi. The ACE Alu polymorphism contributes to neovascular AMD risk. Annual Meeting of the Association of Research in Vision and Ophthalmology (ARVO), Ft. Lauderdale, FL. 2004.
2-D.Lavinsky, S.E. Anorve, A.S. Ratnayake, **H.K. Hamdi**, R.Castellon. Further characterization of secondary sprouting colonies of retinal endothelial cells. Annual Meeting of the Association of Research in Vision and Ophthalmology (ARVO), Ft. Lauderdale, FL. 2004.
3-H.K. Hamdi, R.Castellon. Vitreous: A "bio-brane" with morphogenic properties. Annual Meeting of the Association of Research in Vision and Ophthalmology (ARVO), Ft. Lauderdale, FL. 2004.
4-R.Castellon, S.E. Anorve, A.S. Ratnayake, A.V. Ljubimov, **H.K. Hamdi**. Differential angiogenic potential of retinal endothelial cells from normal, diabetic and diabetic retinopathy patients. Annual Meeting of the Association of Research in Vision and Ophthalmology (ARVO), Ft. Lauderdale, FL. 2004.
5-H.K. Hamdi, S.R. Atilano, J.Reznik1, R.Castellon, J.Tavis, A.B. Nesburn, K.W. Small, C.M. Kenney. Alu DNA Element in the Progesterone Receptor Gene Attenuates Age-related Macular Degeneration . Annual Meeting of the Association of Research in Vision and Ophthalmology (ARVO), Ft. Lauderdale, FL. 2003.
6-R. Castellon, I. Sacerio, S.E. Anorve, A.S. Ratnayake, E. Chang, **H.K. Hamdi**. Secondary sprouting from retinal endothelial cells involves endothelial precursors. Annual Meeting of the Association of Research in Vision and Ophthalmology (ARVO), Ft. Lauderdale, FL. 2003.
7-HK Hamdi, R. Reznik, R. Castellon, S. Atilano, J. Tavis, N. Udar, K, Small, A. Nesburn, M.C. Kenney. DNA polymorphism in ACE gene is protective for Age-related Macular Degeneration. Annual Meeting of the Association of Research in Vision and Ophthalmology (ARVO), Ft. Lauderdale, FL. **2002.**

8-R. Castellon, S.Caballero, **H.K. Hamdi,** A.M. Aoki, M.C. Kenney, M.B. Grant, A.V. Ljubimov. Effects of Tenascin-C on the Angiogenic Potential of Retinal Endothelial Cells. Annual Meeting of the Association of Research in Vision and Ophthalmology (ARVO), Ft. Lauderdale, FL. **2002.**

9- Hamdi HK, Nishio H, and Dugaiczyk. A.Spread of repetitive DNA elements in the primate and human genome.Genome Mapping and Sequencing Conference, Cold Spring Harbor Laboratory, Cold Spring, New York, May 14-May 18, 1997.

10- Sandhu P, **Hamdi HK,** and Dugaiczyk A. Alu elements: Stable, unidirectional insertions in primate genome. (163rd National Meeting of the American Association for the AdvancementOf science: Engaging Science, Sustaining Society, Seattle, WashingtonUSA), AAAS Annual Meeting and Science Innovation Exposition, v163,(1997): A111.

11- Nishio H, **Hamdi H,** Heiskanen M., Palotie A., and Dugaiczyk A.Genomic expansion across the human 4q sub-centromeric region.Genome Mapping and Sequencing Conference, Cold Spring Harbor Laboratory,Cold Spring, New York, May 8-May 12, 1997.

12- Kenney, MC, Brown, DJ, and **Hamdi H.** Proteinase activity in normal human tears: Male-female dimorphism. (Annual Meeting of the Investigative Ophthalmology and Visual Science,Fort Lauderdale, Florida, USA, May 14-19, 1995.)Investigative Ophthalmology& Visual Science, V.36 N4 (1995): S995.

13- Brown, DJ., Bishop, P., **Hamdi H.,** and Kenney MC.Fragmentation of structural components of mammalian vitreous by an endogenousmatrix metalloproteinase.(Annual Meeting of the Investigative Ophthalmology andVisual Science, Fort Lauderdale, Florida, USA, May 14-19, 1995.) InvestigativeOphthalmology & Visual Science, V.36 N4 (1995): S130.

14- Brown, DJ., **Hamdi H.,** Huang, Z-S, and Kenney, MC.Vitreous derived metalloproteinase disrupts the Vitreous structure.(Annual Meeting of the Investigative Ophthalmology and Visual Science,Fort Lauderdale, Florida, USA, May 14-19, 1995.) Investigative Ophthalmology& Visual Science, V.35 N4 (1995): 1459.